Complete Summary

GUIDELINE TITLE

EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy.

BIBLIOGRAPHIC SOURCE(S)

Lauria G, Cornblath DR, Johansson O, McArthur JC, Mellgren SI, Nolano M, Rosenberg N, Sommer C, European Federation of Neurological Societies. EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. Eur J Neurol 2005 Oct;12(10):747-58. [69 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
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BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
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SCOPE

DISEASE/CONDITION(S)

Peripheral neuropathy

GUIDELINE CATEGORY

Diagnosis
Technology Assessment

CLINICAL SPECIALTY

Family Practice
Internal Medicine

Neurology
Pathology

INTENDED USERS

Clinical Laboratory Personnel
Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate the techniques for performing skin biopsy and the choice of biopsy location
- To evaluate the methods for tissue processing and for quantification of intraepidermal nerve fibres (IENF)
- To assess the diagnostic performance of skin biopsy in peripheral neuropathies
- To compare skin biopsy with clinical, neurophysiological, psychophysical, autonomic, and sural nerve biopsy examination
- To recommend European Union (EU) standards
- To propose, if needed, new studies to address unresolved issues

TARGET POPULATION

Patients presenting with peripheral neuropathy

INTERVENTIONS AND PRACTICES CONSIDERED

Punch skin biopsy and quantification of the linear density of intraepidermal nerve fibres (IENF) in at least 50-micrometer thick sections per biopsy, using bright-field immunohistochemistry or immunofluorescence with anti-protein-gene-product 9.5 (anti-PGP 9.5) antibodies

MAJOR OUTCOMES CONSIDERED

Diagnostic efficiency, predictive value, sensitivity, and specificity of skin biopsy and different techniques for tissue processing and nerve fibre evaluation in the diagnosis of peripheral neuropathy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Task Force systematically searched the Medline database from 1989, the year when the first papers reporting immunostaining of human skin with antiprotein-gene-product 9.5 (PGP 9.5) antibodies were published, to 31 March 2005. For each specific issue, the Task Force stored all the articles sorted by the Medline

search, omitted those that were not pertinent, read and rated the remaining articles according to the guidelines of the European Federation of Neurological Societies (EFNS) (see the "Rating Scheme for the Strength of the Evidence" and the "Rating Scheme for the Strength of the Recommendations" fields). In some cases, investigators were asked for original data and methodological details.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

For each specific issue, the Task Force stored all the articles sorted by the Medline search, omitted those that were not pertinent, read and rated the remaining articles according to the guidelines of the European Federation of Neurological Societies (EFNS) (see the "Rating Scheme for the Strength of the Evidence" and the "Rating Scheme for the Strength of the Recommendations" fields). In some cases, investigators were asked for original data and methodological details.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Data extraction was carried out and compared amongst each member of the Task Force. Discrepancies in each topic were discussed and settled during a consensus meeting held in Milan on 8 January 2005. The revised and final version of the guidelines is presented in the original guideline document.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating of Recommendations

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (Hughes RAC, Barnes MP, Baron J, Brainin M [2001]. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces. *Eur J Neurol* 8:549-550).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (class I-IV) supporting the recommendations and ratings of recommendations (A-C) are defined at the end of the "Major Recommendations" field.

Methods to Perform Skin Biopsy and Choice of Biopsy Location

The Task Force members emphasize that the 3-mm punch skin biopsy is a minimally invasive technique. It requires training and is safe as long as sterile procedures and haemostasis are correctly performed. For diagnostic purposes in peripheral neuropathies, performance of a 3-mm punch skin biopsy is recommended. In polyneuropathies, the Task Force recommends performing skin biopsy at the distal leg for quantification of epidermal innervation density. An additional biopsy from the proximal thigh may provide information about a length-dependent process (**level A recommendation**).

Methods to Process Tissue and Quantify Intraepidermal Nerve Fibres (IENF)

For diagnostic purposes in peripheral neuropathies, the Task Force recommends bright-field immunohistochemistry or immunofluorescence with anti-protein-gene-product 9.5 (anti-PGP 9.5) antibodies in 2% paraformaldehyde-lysine-periodate (PLP) or Zamboni's fixed sections of 50 micrometer thickness. For methodological issues on bright-field immunohistochemistry the Task Force refers to McCarthy et al. (1995)*, on immunofluorescence to Wang et al. (1990)**, and on confocal microscopy to Kennedy and Weldelschafer-Crabb (1993)***. Intraepidermal nerve fibres (IENF) should be counted at high magnification (i.e., 40x) in at least three sections per biopsy. The Task Force emphasizes that only single IENF crossing the dermal–epidermal junction should be counted, excluding secondary branching from quantification. The length of the section should be measured in order to calculate the exact linear epidermal innervation density (IENF/mm) (**level A recommendation**).

Further studies are warranted to establish the reliability of the "ocular" method (**level B recommendation**) and the "blister technique" (**level C recommendation**) for quantification of IENF density in peripheral neuropathies.

*McCarthy BG, Hsieh ST, Stocks A et al. (1995). Cutaneous innervation in sensory neuropathies: evaluation by skin biopsy. *Neurology* 45:1848-1855.

**Wang L, Hilliges M, Jernberg T, Wieberg-Edstrom D, Johanson O (1990). Protein gene product 9.5-immunoreactive nerve fibers and cells in human skin. *Cell Tissue Res* 261:25-33.

***Kenney WR, Weldelschafer-Crabb G (1993). The innervation of human epidermis. *J Neurol Sci* 115:184-190.

Diagnostic Performances of Skin Biopsy

Diagnostic efficiency and predictive values of skin biopsy with linear quantification of IENF in the diagnosis of peripheral neuropathy were very high (**level A recommendation**). Immunohistochemical technique does not seem to influence the ability of skin biopsy to demonstrate small fibre sensory neuropathy (SFSN). For diagnostic purposes or as outcome measure in clinical trials the Task Force recommends rigorous quantitative assessment with appropriate quality controls (**level B recommendation**). Cut-off values for epidermal densities in studies based on immunofluorescence microscopy appeared to be higher than in bright-field microscopy studies. Thus far, only the bright-field microscopy method was used to establish normative reference range and diagnostic performances. For quantitative purposes in evaluating peripheral neuropathies, the Task Force recommends determination of IENF density using either immunohistochemistry

with bright-field microscopy or immunofluorescence (**level A recommendation**). Appropriate normative data from healthy subjects matched for age, gender, ethnicity and anatomical site should be used. Quality control should include all the steps of the procedure, in particular, the aspect of intra- and inter-observer ratings.

Studies comparing the diagnostic yield of bright-field microscopy and immunofluorescence with and without confocal microscopy in homogeneous groups of neuropathy patients are warranted. The Task Force emphasizes that the confocal microscopy technique may be useful to investigate cutaneous nerve fibres in demyelinating neuropathies. Furthermore, the diagnostic yield of dermal nerve fibre quantification needs to be addressed. Confocal microscopy technique applied to glabrous skin allows investigation of dermal receptors and their myelinated endings and might provide morphological information that potentially enlarges the usefulness of skin biopsy in sensory neuropathies.

Assessment of Morphological Changes

Quantification of IENF swellings at the lower limb could have a predictive value to the progression of neuropathy, especially if large (**level B recommendation**). Further studies are warranted to establish whether increased IENF swellings could support the diagnosis of sensory neuropathy and whether this morphological change occurs prior to decreasing IENF density. Further studies are also needed to verify whether increased branching is an early diagnostic finding in peripheral neuropathy.

Quantification of Sweat Gland Innervation

Data on sweat gland innervation density in healthy subjects and in patients with peripheral neuropathy as well as data on correlation between sweat gland nerve fibre density and autonomic assessment are limited (**class III evidence**). Although part of the neuropathological examination of skin biopsy, assessment of sweat gland innervation still lacks extensive validation.

Correlation between IENF Density and Clinical, Neurophysiological, Psychophysical, Autonomic, and Sural Nerve Biopsy Examinations

Correlation between IENF density and the severity of neuropathic pain needs extensive validation. Decrease in IENF density might represent a further index to predict poorer outcome in patients with Guillain-Barre syndrome (GBS).

Quantification of IENF density can better assess the diagnosis of SFSN (**level A recommendation**) than sural nerve conduction study (NCS) and sural nerve biopsy. Concordance between IENF quantification and medial plantar sensory nerve action potential (SNAP) amplitude in patients with normal sural NCS suggests that distal sensory nerve recording might be more sensitive than sural NCS in the diagnosis of sensory neuropathy.

The inverse correlation between IENF density and warm threshold assessed by quantitative sensory testing (QST) in patients with SFSN demonstrates that both methods can reliably assess the impairment of unmyelinated nerve fibres in

peripheral neuropathies (**level A recommendation**). Correlation with heat-pain and cooling thresholds as well as measures of autonomic dysfunction needs more extensive validation (**level C recommendation**).

Studies of Skin Reinnervation

Skin biopsy with quantification of IENF density can be used to assess the regeneration rate of sensory axons in peripheral neuropathies and could represent a potential outcome measure in clinical trials (**level B recommendation**).

European Union Standards

Skin biopsy is a reliable technique to assess loss and regeneration of sensory nerve fibres in peripheral neuropathies. For diagnostic purposes, the Task Force endorses 3 mm punch skin biopsy at the distal leg, and quantification of linear epidermal innervation density in at least three 50-micrometer thick sections per biopsy, fixed in 2% paraformaldehyde-lysine-periodate or Zamboni's solution, by immunohistochemistry using anti-PGP 9.5 antibodies and bright-field microscopy or immunofluorescence with or without confocal microscopy.

The Task Force strongly recommends training in an established cutaneous nerve laboratory before performing and processing skin biopsies in the diagnosis of peripheral neuropathies. Appropriate normative data from healthy subjects matched for age, gender, ethnicity and anatomical site should be always used. Quality control should include all the steps of the procedure, in particular, the aspect of intra- and inter-observer ratings for qualitative assessments and for quantitative analysis of epidermal densities.

Definitions:

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

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Rating of Recommendations

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Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of skin biopsy in the diagnosis of peripheral neuropathy

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.
- Data on sweat gland innervation density in healthy subjects and in patients with peripheral neuropathy as well as data on correlation between sweat gland nerve fibre density and autonomic assessment are limited. Although part of the neuropathological examination of skin biopsy, assessment of sweat gland innervation still lacks extensive validation.
- Correlation of intraepidermal nerve fibres (IENF) density with the severity of neuropathic pain, heat-pain and cooling thresholds, as well as measures of autonomic dysfunction needs more extensive validation.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

IMPLEMENTATION TOOLS

Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Lauria G, Cornblath DR, Johansson O, McArthur JC, Mellgren SI, Nolano M, Rosenberg N, Sommer C, European Federation of Neurological Societies. EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. Eur J Neurol 2005 Oct;12(10):747-58. [69 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 Oct

GUIDELINE DEVELOPER(S)

European Federation of Neurological Societies - Medical Specialty Society

SOURCE(S) OF FUNDING

European Federation of Neurological Societies

GUIDELINE COMMITTEE

European Federation of Neurological Societies Task Force

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

No member of the Task Force has conflict of interest in this report.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available to registered users from the European Federation of Neurological Societies Web site.

Print copies: Available from Giuseppe Lauria, MD, Immunology and Muscular Pathology Unit, National Neurological Institute 'Carlo Besta', Via Celoria, 11, 20133 Milan, Italy; Phone: +39 02 2394 2255; Fax: +39 02 7063 3874; E-mail: glauria@istituto-besta.it

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS

scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site.

- Guideline papers. European Federation of Neurological Societies. Electronic copies: Available from the European Federation of Neurological Societies Web site.
- Continuing Medical Education questions available from the European Journal of Neurology Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on December 6, 2006. The information was verified by the guideline developer on January 15, 2007.

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